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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/00, 9/16, 47/48, 31/465

A1

(11) International Publication Number: WO 94/27576

(43) International Publication Date: 8 December 1994 (08.12.94)

(21) International Application Number: PCT/GB94/01092

(22) International Filing Date: 20 May 1994 (20.05.94)

(30) Priority Data:
9310412.3 20 May 1993 (20.05.93) GB

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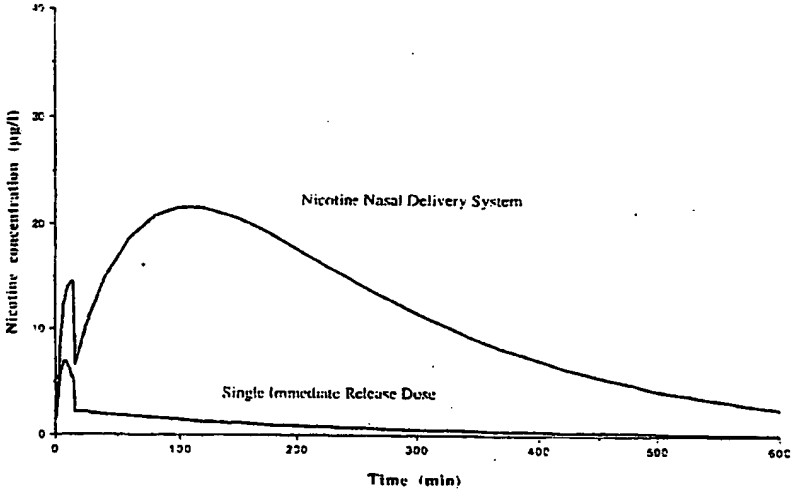
(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NASAL DRUG DELIVERY COMPOSITION CONTAINING NICOTINE



(57) Abstract

The present invention provides a nasal drug delivery composition comprising nicotine or a pharmacologically-acceptable salt or derivative thereof wherein the composition is adapted to delivery a pulse of nicotine for rapid absorption and a controlled release of nicotine for subsequent sustained absorption. The controlled release phase can be achieved by providing an ion-exchange material which will form a complex with the nicotine. The ion-exchange material may be a polymeric material such as a polysaccharide, or may be in the form of bioadhesive ion-exchange microspheres. The pulse release can be achieved by overloading the ion-exchange material with nicotine so that the composition contains some excess nicotine for immediate release and absorption. Alternatively, some nicotine may be associated with a non ion-exchange material which will release the nicotine immediately on contact with the nasal mucosa, for example non-ion-exchange bioadhesive microspheres.

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NASAL DRUG DELIVERY COMPOSITION CONTAINING NICOTINE

The present invention relates to compositions for nasal administration and, more particularly, to compositions for nasal administration of nicotine.

Smoking remains the single most important preventable cause of death in modern society. It can be estimated that in the US alone more than 430 000 deaths in 1988 were attributable to cigarette smoking. At least nine out of ten smokers are to some extend dependent upon nicotine and 75% are moderately to strongly dependent and continue smoking despite attempts to stop. In the United States the strong interest in stopping smoking is demonstrated by the fact that nearly 20 million people try to quit smoking each year. Their need for additional help can be seen in the fact that more than 90% fail to maintain their abstinence.

The major problem with nicotine is that it is highly addictive. Nicotine fulfils all criteria of an addictive drug, it is psychoactive, it affects the mood, it can act as a primary reinforcer, it induces tolerance, and physical as well as psychological changes occur on withdrawal.

Importantly, there is no direct evidence that nicotine itself is carcinogenic or mutagenic, nor does it act as a tumour initiator, promoter or co-carcinogen. Similarly, none of the major metabolites of nicotine are known to be carcinogenic. In contrast, tobacco and especially tobacco smoke contains several potent carcinogens.

A major limiting factor in the successful use of nicotine replacement therapy for smoking cessation is the lack of an appropriate delivery

system. When a person smokes a cigarette, the level of nicotine rise rapidly in the blood and in the brain with an interval of just 10-20 seconds between taking a puff and the nicotine arriving in the brain. The presently marketed nicotine replacement products, the transdermal nicotine patch and the nicotine chewing gum, are not entirely satisfactory in that they do not provide the patient with the nicotine "buzz" associated with smoking a cigarette, since they are both slowly acting controlled release systems where only low nicotine plasma levels are obtained. Hence clinical trails have shown that only about 20% - 30% of those smokers who have used nicotine patches and nicotine chewing gum successfully quit smoking after one year compared to 15% of those smokers receiving behavioural support alone.

Transdermal patches seem to be no more effective than placebo in maintaining smoking cessation in the long term. The long term results after the use of patches alone have not been impressive Medical letter (Vol. 34, p37, 1992).

The nicotine chewing gum is a slow release preparation where the rate of release of nicotine will depend on the rate of chewing. It takes 20-30 min of vigorous chewing to release 95% of the nicotine content of the gum. Without chewing or if the gum is accidently swallowed negligible amounts of nicotine are released. The gum contains 2 or 4 mg of nicotine. A typical smoker needs about 15 pieces of gum a day. The gum has an unpleasant taste and may be irritating to the mouth and throat. Potential side effects are heartburn and hiccups. Tired and aching jaws may be experienced from intensive chewing and users rarely maintain blood nicotine concentrations above one third of their levels from smoking. The chewing gum is contraindicated in individuals with gastritis or active peptic ulcer disease and presents difficulties for those wearing dentures.

US 3877468, US 3901248 and US 3845217 discloses a chewing gum comprising nicotine in the form of a complex with an insoluble cation-exchange base.

The nicotine patch placed on the skin will give a steady release of nicotine over 24 hours and should be changed daily. The patch is available in three sizes delivery about 21, 14 and 7 mg/24 hours) With the patch in place it takes 3 - 4 hours to attain significant blood levels of nicotine. The continuous dosing provided by patches can disrupt the usual day/night variation in nicotine intake provided by smoking and can result in a total dose of nicotine per 24 hour exceeding the normal smoking dose. Moreover it seems that if nicotine is given both night and day compared to only daytime, sleep disturbances and nightmares can result. A potential side effect of the patch is skin irritation. A further disadvantage with the nicotine patch is that it is a passive system and for some individuals, a closer involvement with the treatment is to be preferred.

Thus, neither the nicotine patch system nor the nicotine chewing gum system can be considered to be satisfactory for nicotine replacement therapy and smoking cessation.

It is well established that nicotine is easily absorbed nasally. Nicotine concentrations in the blood of regular users of dry snuff are similar to those of cigarette smokers and peak concentrations after a single pinch of snuff is reached in a time similar to that for smoking a cigarette. The absolute bioavailability of nicotine applied to different nasal regions has been measured by Johansson et al. (1991) in man. Single doses of 1 mg were given and plasma concentrations followed over 6 hours. Bioavailability, as compared to IV infusion was 60 to 75%. The rate of absorption was fast. the maximum concentration being reached within

about 10 minutes. No differences could be found for different nasal treatments.

Nasal sprays containing nicotine have been suggested as an alternative approach for smoking cessation. The prior art has described various devices for the better delivery of nicotine. For example WO 8703813 a spray device with an electronic timer restricting doses to a predetermined number per session is described. A nasal aerosol spray supplying nicotine for anti-smoking therapy is mentioned as an advantage. In US 4655231 an improved snuff for nasal application of nicotine containing a pure nicotine salt, a water soluble diluent and colouring and flavouring is described. The water soluble diluent is preferably an organic acid. The mixture allows rapid application of nicotine. GB 2133691 describes an aqueous solution of nicotine or a non-toxic salt of nicotine together with a non-irritating thickening agent. The composition has a pH of 2-6 and has a viscosity of at least 100 CP. The thickening agent is a natural or synthetic polymer or an oil substance comprising the oil phase of an emulsion. A nicotine solution with a viscosity less than 100 CP has been mentioned in RD 239015. WO 91/09599 discloses a smoking substitute for sublingual administration comprising a nicotine-cyclodextrin complex. The composition is stated to have improved stability and taste, pH independent release and reduced irritant sensation. It is also suggested that the composition could be given nasally.

The nasal nicotine systems discussed above were designed to give rapid absorption of nicotine, followed by a rapid decrease in the level of absorbed nicotine, mimicking the effect of smoking a cigarette. More recently, Sutherland et al. 1992, suggested that the rapid absorption of the nicotine when given nasally may be an important factor for smokers for whom other forms of replacements are too slow. Although nasal nicotine

spray systems will provide the desired "buzz" effect, the benefit is short lived and will necessitate frequent dosing. This will be unacceptable to the potential user.

The pharmacokinetics of nicotine in man has been described in some detail (for example see Benowitz 1990). The importance of including features associated with tolerance has been stressed. For example in the end of the day the response of the cigarette is blunted owing to the development of tolerance. Tolerance can develop and regress in cycles throughout the day. Because of dose response and tolerance characteristics, habitual smokers need to smoke at least 15 cigarettes and consume 20-40 mg of nicotine per day to achieve the desired effect of cigarette smoking and to minimise withdrawal discomfort. The dose of systemically available nicotine absorbed by regular smokers averages about 1 mg per cigarette. The daily nicotine intake of smokers averages about 25 mg. Two minutes after the first cigarette the plasma nicotine level reaches about 13 μg/l. The nicotine peak plasma levels of regular smokers of 15 or more cigarettes per day average about 35 μg/l during daytime.

We have now found that an improved nicotine replacement formulation can be achieved by providing a nasal composition which provides both an initial rapid release and absorption of nicotine, a pulse effect, followed by a controlled release and absorption of nicotine to provide a sustained high level of absorbed nicotine. The invention therefore provides a nasal drug delivery composition comprising nicotine or a pharmacologically acceptable salt or derivative thereof in which the nicotine or nicotine salt or derivative is released as a pulse followed by a controlled release phase. The pulse effect provides an initial rapid peak in plasma nicotine levels which gives the "buzz" effect of smoking a cigarette. The controlled release phase then provides a more gradually increased and maintained

high plasma level of nicotine, removing the craving for further nicotine, and avoiding the need to use the composition at frequent intervals.

The controlled release effect can be achieved by providing an ion-exchange material in the composition. By ion-exchange material we mean a natural or synthetic material comprising ionisable groups and which have the ability to exchange ions attracted to their ionised groups with ions of the same charge present in solution. Nicotine is a basic drug and when ionised it carries a positive charge. The ion-exchange material must therefore be one which when ionised releases a positive ion leaving a negative charge to which the ionised nicotine is attracted. The ion-exchange material forms a complex with the ionised nicotine and releases the nicotine slowly when in contact with the nasal mucosa.

The ion-exchange capacity of the ion-exchange material used should preferably be in the range 0.01-50 milli equivalents/g, more preferably 0.1-20 meq/g and most preferably 0.2-10 meq/g.

The ion-exchange material is preferably bioadhesive to aid its retention in the nasal cavity. By bioadhesive we mean a material which will adhere to the surface of the nasal cavity. The ion-exchange material gradually releases nicotine providing a controlled release and uptake of nicotine across the nasal mucosa.

Natural or synthetic nicotine may be used or a pharmacologically-acceptable salt or derivative of nicotine. Nicotine forms water soluble salts and double salts with many metals and acids. The use of salt forms of nicotine avoids the problems associated with the free base form of nicotine includes losses due to volatility and decomposition in the presence of oxygen. Preferred salts for use in the invention includes nicotine

dihydrogen tartrate, nicotine tartrate, nicotine hydrochloride, nicotine oxalate, nicotine hydrogen tartrate, nicotine dihydrochloride, nicotine sulphate, 2-methyl nicotine and other nicotine derivatives. Nicotine dihydrogen tartrate or nicotine tartrate are especially preferred and also 2-methyl nicotine which has reduced side-effects on the heart. Unless otherwise stated, all amounts of nicotine stated are calculated as the equivalent amount of nicotine free base.

The pulse release of nicotine may be achieved by providing a material which is not an ion-exchange material. The nicotine associated with this material will then be released immediately on contact with the nasal mucosa for rapid absorption. Alternatively, excess nicotine is provided in the composition so that the ion-exchange material is overloaded with nicotine. The excess nicotine not bound by the ion-exchange material is available for immediate uptake on contact with the nasal mucosa. This excess nicotine is also referred to throughout as "free nicotine".

Monovalent cations can also be included in the composition to compete with the nicotine for binding with the ion-exchange material, thus ensuring that some of the nicotine is left as free nicotine. Such cations should be non-toxic and pharmacologically acceptable, for example sodium, calcium and ammonium.

The ion-exchange material may be in the form of bioadhesive microspheres, or may be an aqueous solution, suspension or freeze-dried preparation of a polymeric material.

It has previously been shown that bioadhesive microspheres are able to increase the residence time of a formulation in the nasal cavity thereby increasing the time available for absorption of the drug (Illum et al, 1987).

It was also shown by Illum et al. (1988) that such a system was able to increase the absorption of the antibiotic agent, Gentamicin thereby allowing it to be given via the nasal route rather than by injection.

The use of the bioadhesive microspheres in drug delivery compositions for transmucosal administration has been described in WO 88/09163 and WO 89/03207.

The slow release of drugs and model compounds from ion-exchange microspheres has been the subject of previous work (Illum and Davis, 1982; US Patent 4847091). Here the strong binding of the drug to the microspheres via a process of ionic interaction has been used to modify drug release rates. The applications described were for parenteral administration and the local administration of an anionic drug sodium cromoglycate to the nasal cavity. Various ion-exchange microsphere systems are described in the prior art (for example see Kown et al. (1990), Cremers et al (1990) and Codde et al (1990)). None of these systems has been used nasally for nicotine administration.

The ion-exchange microspheres suitable for use in the present invention are microspheres which carry suitable anionic groups such as carboxylic acid residues, carboxymethyl groups, sulphopropyl groups and methylsulphonate groups. Carboxylated starch microspheres are especially preferred. Other materials include hyaluronic acid, chondroitin sulphate, alginate, heparin and heparin-albumin conjugates, as described in Kwon et al. (1991) albumin-poly (α-L glutamic acid), albumin-poly (aspartic acid) or ion-exchange albumin microcapsules as described by Savaya et al (1987). Ion-exchange resins (cation exchangers) can also be used such as Aminex-A-6 (Biorad)-a resin containing sulphonate groups or those with carboxymethyl or sulphopropyl groups. Cation exchanges which can be

used include carboxymethyl dextran (CM Sephadex™) and sulphopropyl dextran (SP Sephadex™) carboxymethyl agarose (CM Sepharose™), carboxymethyl cellulose, cellulose phosphate, sulphoxyethyl cellulose, agarose (Sepharose), cellulose beads (Sephacel) and dextran beads (Sephadex) (all available from Pharmacia) are materials which such functional groups. Carboxylated starch microspheres (Cadexomer) are available from Perstorp.

Cation exchangers on polystyrene include the Amberlite and Dowex strongly acidic cation exchangers and the Amberlite weekly acidic cation exchangers as described in the Sigma Chemical Co Ltd catalogue, 1993, p1591-1593. The Amberlite strongly acidic cation exchangers have sulphonic acid functional groups and the weakly acidic ones have carboxylic acid functional groups. The Dowex exchanger has nuclear sulphonic acid functional groups.

The ion-exchange microspheres can be used with free nicotine to provide both the fast pulse release of nicotine and the controlled release, or can be mixed with non-ion-exchange microsphere. Nicotine is adsorbed to the surface of the non-ion-exchange microsphere and will be released quickly on contact with the nasal mucosa to provide the pulsed effect. Suitable materials for use as non-ion-exchange microspheres include starch, gelatine, collagen and albumin. When a mixture of ion exchange and non-ion-exchange microspheres are used, the composition should contain between 50:1 and 1:1 of ion-exchange to non-ion-exchange microspheres, preferably 25:1 to 5:1 and more preferably 10:1.

The term microsphere as used herein is defined as substantially spherical particles which can be a monolithic solid sphere or in the form of a small capsule. To ensure correct deposition in the nasal cavity, the

microspheres should preferably be of a size between 0.5 and 250μm, more preferably 10-100μm.

The microspheres can be made by procedures well known in the art including spray drying, coacervation and emulsification (see for example Davis et al, Microsphere and Drug Therapy, Elsevier, 1984). For example, starch microspheres were prepared by an emulsion technique as follows:

5g potato starch were dissolved in 95ml of water at about 90°C. A second solution was prepared from 3g of polyethylene glycol (M_w = 6000) and 46ml of water. This solution was heated to about 70°C, whereafter the warm starch solution was added while stirring, to form an emulsion. When the two-phase system had formed (with the starch solution as the inner phase) the mixture was allowed to cool to room temperature under continued stirring, wherewith the inner phase was converted to gel particles. The particles were filtered off at room temperature and slurried in 100ml of ethanol, whereafter the particles were again filtered off and laid to dry in air.

The yield was 90%.

Soluble potato starch microspheres was prepared by a coacervation technique as follows:

15ml 5% starch solution (pH=7) was kept at a constant temperature of 70°C and stirred (500rpm) while a 30% solution of polyethylene glycol was added (~7 ml) until phase separation had occurred, the system was stirred for further 15 min before it was cooled on ice during constant stirring. The microspheres were then isolated by filtration and freeze-

dried. With a stirring speed of 500rpm particles with a mean size of 33μm $\pm$ μm was produced.

The ion-exchange microspheres can be made from suitable ion-exchange material which already contains the appropriate functional groups, or non-ion-exchange microspheres of suitable materials can then be functionalised by methods well known in the art to provide ion-exchange microspheres.

For the microsphere compositions of the invention, a nicotine salt should preferably be used to ensure that the nicotine is in its ionised form. The nicotine or nicotine salt is adsorbed to the microspheres by admixing with the microspheres after their formation.

The microspheres, both ion-exchange and non-ion-exchange can be hardened by well known cross-linking procedures such as heat treatment or by using chemical cross-linking agents. Suitable agents include dialdehydes, including glyoxal, malondialdehyde, succinicaldehyde, adipaldehyde, glutaraldehyde and phthalaldehyde, diketones such as butadione, epichlorohydrin, polyphosphate and borate. Dialdehydes are used to cross-link proteins such as albumin by interaction with amino groups, and diketones form schiff bases with amino groups. Epichlorohydrin activates compounds with nucleophiles such as amino or hydroxyl to an epoxide derivative. The cross-linkers used for the ion-exchange microspheres should not be directed towards the relatively charged groups required for binding the nicotine.

The microsphere composition can be produced as a freeze-dried formulation and administration nasally by the usual methods, for example by using a nasal insufflator. Such devices are well known.

As another alternative embodiment, the composition may comprise solely non-ion-exchange microspheres. In this case the nicotine or nicotine salt is incorporated into the microsphere during its formulation, and this incorporated nicotine will then be released from the microsphere gradually to provide the controlled release effect. Excess nicotine is then mixed with the microspheres after their formulation and adsorbs to the microsphere as before. This nicotine will, as described above, be released from the microsphere immediately on contact with the nasal mucosa to provide the pulse effect.

Nicotine can be incorporated into a non-ion-exchange microsphere for example as follows:

Human serum albumin based microspheres containing nicotine were prepared by an emulsification technique; 75.0ml of cotton seed oil was mixed with 25.0ml of petroleum ether and stirred for 10 min in a 200.0ml beaker using a magnetic stirrer. Nicotine was dissolved in the HSA solution (2, 3 or 5% w/v), to obtain drug solution (2%) in aqueous phase. The aqueous phase containing HSA and nicotine was added to the ethereal solution of cotton seed oil dropwise with continuous stirring using a mechanical stirrer at 1000 rpm for 15 min. The microspheres were stabilized by adding 0.1ml of 25% w/v glutaraldehyde solution with continuous stirring for 15 min or by adding the emulsion system to preheated cotton seed oil (100.0ml) at 120°C dropwise with continuous stirring. The microspheres were separated by centrifugation at 3000 x g for 15 min and washed with petroleum ether three times for complete removal of oil adhering to the microsphere surface. The microspheres were filtered using Millipore filter and again washed with petroleum ether and ethanol. Preparation were freeze-dried and stored frozen until used in further studies. For 1 dose, using a 2, 3 or 5% w/v HSA solution, 30,

40 or 50mg of nicotine containing microspheres were mixed with for example, 2mg of nicotine or freeze dried in an aqueous solution containing 2mg nicotine.

The composition of the invention may also be a liquid formulation comprising a polymeric ion-exchange material. The polymeric material should provide a negatively charged group as discussed above and also should provide a viscous solution to aid retention in the nasal cavity. Preferably the material will gel when in contact with the nasal mucosa.

Suitable polymeric materials include gellan gum, welan, rhamsan, alginate, carboxymethylcellulose, sodium alginate, xanthan, agar, guar derivatives such as carboxymethyl guar gum, carageenan, dextran sulphate, keratan, dermatan, pectin. Polysaccharides and derivatives are particularly suitable ("Polysaccharides and derviatives" edited by R C Whistler and J N BeMiller (3rd Ed.) Academic Press, San Diego 1993).

A preferred material is gellan gum, which is the deacetylated form of the extracellular polysaccharide from Pseudomonas elodae. Native/high-acyl gellan is composed of a linear sequence of tetra-saccharide repeating units containing D-glucuronopyranosyl, D-glucopyranosyl and L-rhamnopyranosyl units and acyl groups.

Another preferred material is alginate. Alginate is composed of two building blocks of monomeric units namely β-D-mannuronopyranosyl and α-guluronopyranosyl units. The ratio of D-mannuronic acid and L-guluronic acid components and their sequence predetermines the properties observed for alginates extracted from different seaweed sources.

Welan is produced by an Alcaligenes species. Welan has the same basic

repeating unit as gellan but with a single glycosyl sidechain substituent. The side unit can be either an α-L-rhamnopyranosyl or an α-L-mannopyranosyl unit linked (1→3) to the 4-0-substituted β-D-glucopyranosyl unit in the backbone.

Rhamsan is produced by an Alcaligenes species. Rhamsan has the same repeating backbone unit as that of gellan but with a disaccharide side chain on O-6 of the 3-O-substituted β-D-glucopyranosyl unit. The side chain is a β-D-glucopyranosyl-(1-6)-α-D-glucopyranosyl unit.

Xanthan is produced by a number of Xanthomonas strains. The polymer backbone, made up of (1→4)-linked β-D-glucopyranosyl units is identical to that of cellulose. To alternate D-glucosyl units at the 0-3 position, a trisaccharide side chain containing a D-glucoronosyl unit between two D-mannosyl units is attached. The terminal β-D-mannopyranosyl unit is glycosidically linked to the 0-4 position of the β-D-glucopyranosyluronic acid unit, which in turn is glycosidically linked to the 0-2 position of an α-D-mannopyranosyl unit.

Carrageenan is a group of linear galactan polysaccharides extracted from red seaweeds of the Gigartinaceae, Hypneaceae, Solieriaceae, Phyllophoraceae and Furcellariaceae families that have an oster sulfate content of 15-40% and contain alternatively (1→3)-α-D- and (1→4)-α-D-glycosidic linkages.

Agar is a hydrophilic colloid extracted from certain marine algae of the class Rhodophyceae where it occurs as a structural carbohydrate in the cell walls (see also Kang and Pettitt: Xanthan, Gellan, Welan and Rhamsan in Industrial gums by Whistler and BeMiller (Eds), Academic Press Inc. London, 1993).

Mixtures of gellan with other polymers such as alginate can be used, gelling of the mixture being caused by the gellan gum. Other combinations of gums can also be used, particularly where the combination gives a synergistic effect, for example in terms of gelation properties. An example is xanthan - locust bean gum combinations.

The advantage of gellan over other materials is that it can be administered as a fluid system but in the nasal cavity the system will gel, thereby providing a bioadhesive effect and holding the drug at the absorptive surface for an extended period of time.

The grade of gellan gum can be Gelrite or Kelcogel from Kelco Int, Ltd. or other similar grades from other manufacturers. The gellan can be prepared at a concentration of 0.1 w/v to 15% but a preferred range of concentrations is 0.2% to 1%.

For gelling to occur, particularly of gellan gum, monovalent or divalent cations must be present in the composition.

Suitable cations include sodium, potassium, magnesium and calcium. The ionic concentration is chosen according to the degree of gelling required, and allowing for the effect that the ionised drug present may have on gelling. At a 0.2% gum concentration, the divalent ions, calcium and magnesium give maximum gel hardness and modulus at molar concentrations approximately one fortieth (1/40) of those required with the monovalent ions, sodium and potassium. A finite concentration of each cation is required to induce gelation. For the nasal formulations of the invention the ionic strength is kept sufficiently low to obtain a low viscosity formulation but sufficiently high to ensure gelation once administration into the nasal cavity where gelation will take place due to

the presence of cations int he nasal liquid. The ionic strength for a 0.5% gellan gum can be in the range of 0.1mM - 50mM for monovalent cations with the preferred range being 1mM - 5mM and 0.1mM - 5mM for divalent cations with the preferred range being 0.15mM - 1mM. For higher concentrations of gellan gum the ionic strengths should be lowered accordingly. The cations will complete with the positively charged nicotine for binding with the polymeric material, and whilst this may be desirable to a certain degree to ensure the presence of free nicotine in the composition, the concentration of cations should be controlled so that sufficient nicotine will bind with the ion-exchange polymeric material.

The complex between nicotine and the ion-exchange material forms as a result of ionic interaction between the negatively charged polymeric material and the positively charged nicotine. The pH of the composition must therefore be such that the two species are fully ionised. The pH should be kept in the range pH 3 to 8, preferably pH 4 to 6, by the presence of appropriate buffers or acids. For these ion-exchange materials the nicotine can be added either as nicotine itself or as a nicotine salt or derivative as the control of the pH by the addition of appropriate acids will ensure that the nicotine is in its ionised form.

The liquid formulations are administered using well-known nasal spray devices. If the formulations are freeze-dried, they can be administered using a nasal insufflator, as for the microsphere preparations.

In a liquid formulation, the polymeric ion-exchange material will typically be provided in a concentration of from 0.01% to 20%, preferably 0.05-10%, more preferably 0.1% - 5%.

The compositions of the invention can also contain any other

pharmacologically-acceptable, non-toxic ingredients such as preservatives, antioxidants, flavourings etc. Benzalkonium chloride may be used as a preservative. However, as this is positively charged, it will complete with the ionised nicotine for binding with the ion-exchange material and can therefore be used to regulate the nicotine binding and ensure the presence of free nicotine for the pulse absorption.

The nicotine or nicotine salt or derivative should be present in an amount to provide a ratio of between 50:1 to 1:1, preferably 25:1 to 2:1, most preferably 15:1 to 5:1 of nicotine bound to the ion-exchange material and free nicotine or nicotine bound to the non-ion exchange material calculated as the equivalent nicotine free base. The amount of nicotine or salt or derivative used will be chosen according to the dose required, but the composition will typically deliver an initial pulse of 0.2 to 3mg, preferably 1mg, equivalent nicotine free base for rapid absorption and 5-20mg, preferably 10mg equivalent nicotine free base released in a controlled manner for sustained absorption. The composition should preferably deliver the pulse of nicotine for absorption over a period of 30 minutes, preferably 20 minutes and more preferably 10 or 5 minutes after administration. The composition should preferably deliver controlled release of nicotine for absorption over a period of 12 hours, preferably 10 hours and more preferably 6 hours following administration. For a liquid formulation the concentration of nicotine in the formulation, calculated as the equivalent free base would be 1-20%, preferably 1-10%, more preferably 2-7%. For a freeze-dried powder or microsphere preparation, the concentration would be 1-75%, preferably 2-50%, more preferably 5-25%. The formulations would typically be administered every six hours. However the composition will provide for more extended periods between administration, say 10 hours, for night time use.

Specific embodiments of the invention will now be described in the following examples and with reference to the Figures in which:

Figure 1 is a computer generated curve of the time course of nicotine concentration in the body compartment of the model system following intranasal administration of a composition according to the invention, containing 1000μg nicotine for immediate release and 10000μg for controlled release, compared to that of a single immediate release dose of 1000μg alone;

Figure 2 is a Franz diffusion cell; and

Figure 3 is a closed loop system containing a Franz diffusion cell.

In the present invention it has been found that an improved nicotine replacement therapy can be achieved by a nasal nicotine composition which provides a two phase release and absorption of nicotine - an initial rapid pulse of nicotine followed by a controlled release phase.

Computer modelling studies have shown the pattern of nicotine levels that will be achieved with such a system and this is shown in Figure 1. From this it will be seen that the composition of the invention provides a nicotine profile which shows an initial sharp peak of nicotine absorption followed by a larger but more gradual and sustained peak. This is in contrast to the sharp but rapidly decreasing peak found with a single immediate release dose of nicotine achieved for example with the currently known nasal nicotine delivery systems or seen when smoking a cigarette.

Specific embodiments of the invention are shown in the following examples.

Example 1

Starch microspheres (Eldexomer) and starch microspheres that carried carboxyl groups (Cadexomer) were obtained from Perstorp Fine Chemical Companies, Sweden. The microspheres had a particle size in the range of 53-106 micron diameter in the unswollen state. The microspheres (5g) at a ratio of 10:1 carboxylated to non-carboxylated were mixed with 20ml of an aqueous solution of nicotine (pH adjusted to 7) at a concentration of 5%. The system was freeze dried and doses of 50mg powder were packed into gelatin capsules for administration by a nasal insufflator device. The immediate release component was 1mg and the controlled release component 9mg.

Example 2

An aqueous solution was prepared containing 25mg/ml of sodium alginate and 2mg/ml gellan gum using heating to 70°C and continuous stirring. Nicotine dihydrogen tartrate to give a final concentration of 75mg/ml was added. The system was mixed for 6 hours to allow interaction between the gellan and the nicotine.

Example 3

A nicotine-alginate complex that can provide controlled release of nicotine in the nasal cavity can be prepared by mixing a solution of sodium alginate and nicotine dihydrogen tartrate. The concentrations of the alginate and nicotine are chosen to provide a 1:1 stoichiometric complex. The complex together with a suitable dose of free nicotine salt that will provide the pulse release phase can be administered nasally as a viscous solution or can be dried (for example by standard

procedures of freeze or spray drying) and administered as a powder or a suspension. Such powder complex can be administered as the material itself or in combination with bioadhesive microspheres and powders as described by Illum et al. 1987, 1988.

4.6g of nicotine dihydrogen tartrate (Sigma) was dispersed in 100ml of distilled water containing 1.75g of sodium alginate (low molecular weight grade - Protan Laboratories) by stirring over a period of 24 hours. The nicotine - alginate complex was recovered by a process of freeze drying. Other grades of alginate can also be used.

Example 4

An aqueous solution was prepared containing 20mg/ml of sodium alginate and 51mg/ml of nicotine dihydrogen tartrate. This concentration of nicotine salt was equivalent to 18mg/ml of nicotine base.

The release of nicotine from this formulations was measured using a Franz diffusion cell apparatus (see Figure 2). The Franz diffusion cell as shown in Figure 2 comprises:

1 - sample compartment
2 - metal clasp to secure membrane
3 - flange cap
4 - membrane
5 - water jacket
6 - feed from water bath
7 - exit to water bath
8 - stirrer

9 - eluant outlet (to cuvette)

10 - eluant inlet from peristaltic pump

The system in Figure 3 comprises:

11 - sample inlet

12 - Franz cell

13 - flow through cuvette

14 - UV spectrophotometer

15 - printer

16 - peristaltic pump

Twenty microlitres of formulation (equivalent to 0.36 mg of nicotine) were applied to the membrane in the sample compartment (0.45 μm cellulose nitrate membrane). Drug diffused across the membrane into the diffusion cell which contained a stimulated nasal electrolyte solution (150mEq/l Na^+, 40 mEq/l K^+, 8 mEq/l Ca^{2+}). The solution was continuously circulated through a flow cell and the appearance of nicotine monitored spectrophotometrically.

The release characteristics of the formulation indicated a biphasic profile demonstrating initial pulse release followed by a sustained release phase.

Example 5

Into a 10ml glass vial was weighed 50mg of Amberlite IR 120 ion-exchange resin (Rohm & Haas, Philadelphia). The resin was suspended in 3.33ml of an aqueous solution containing a total of 15.4 mg of nicotine dihydrogen tartrate (equivalent to 5mg of nicotine base). The mixture was frozen in liquid nitrogen and lyophilised and mixed with 2mg of (free)

nicotine dihydrogen tartrate.

Example 6

Into a 10ml glass vial was weighed 50mg of Amberlite IR 120 ion-exchange resin (Rohm & Haas, Philadelphia). The resin was suspended in 3.33ml of an aqueous solution containing a total of 30.8mg of nicotine dihydrogen tartrate (equivalent to 10mg of nicotine base). The mixture was frozen in liquid nitrogen and lyophilised.

Example 7

A solution of gellan at a concentration of 0.2% w/w was prepared by dispersing 20mg gellan gum in 10ml of distilled water and heating to 70°C during continuous stirring until the gellan gum was dissolved. Nicotine tartrate to give a final concentration of 3.5% was added. The system was mixed for 6 hours to allow interaction between the gellan and the nicotine.

Example 8

It is possible to prepare combinations of microsphere materials. Into a 10ml glass vial were weighed 50mg of Eldexomer starch (non-carboxylated) microspheres (Perstorp, Sweden). These are non-ion-exchange microspheres. The microspheres were suspended in 3.33ml of an aqueous solution containing a total of 15.4mg of nicotine dihydrogen tartrate (equivalent to 5mg of nicotine base). The mixture was frozen in liquid nitrogen and lyophilised.

The release characteristics of the lyophilised formulation were measured using the Franz diffusion cell. A rapid release profile was found. One

part of the Eldexomer microsphere nicotine preparation was mixed with an equal proportion of the microsphere preparation described in Example 5. The release demonstrated a pulse release of nicotine followed by a slower release phase. In this manner by mixing microspheres of different properties it is possible to obtain different release profiles for intended use in vivo.

Besides using in smoking cessation or as a nicotine replacement, the novel nasal delivery systems for nicotine herein described could also be useful when it is required to dose nicotine for therapeutic reasons. These include its use as a cognitive enhancer in ulcerative colitis, weight reduction, Parkinsons disease, Alzheimers disease, narcolepsy, depression, sleep apnoea.

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CLAIMS

1. A nasal drug delivery composition comprising nicotine or a pharmacologically-acceptable derivative or salt thereof, characterised in that the composition is adapted to deliver a pulse of nicotine for rapid absorption and a controlled release of nicotine for subsequent sustained absorption.

2. A composition according to claim 1 which further comprises an ion-exchange material which forms a complex with the nicotine or salt or derivative and provide the controlled release of nicotine.

3. A composition according to claim 2 wherein the ion-exchange material is in the form of microspheres.

4. A composition according to claim 3 wherein the microspheres comprise carboxylated starch alginate or albumin-heparin conjugates.

5. A composition according to claim 3 wherein the microspheres comprise an ion-exchange resin.

6. A composition according to any one of claims 3 to 5 wherein the composition further comprises non ion-exchange microspheres to provide the pulse release of nicotine.

7. A composition according to claim 2 wherein the ion-exchange material is a polymer containing ionizable groups.

8. A composition according to claim 7 wherein the ion-exchange polymer is gellan, alginate or a mixture of alginate and gellan.

9. A composition according to claim 7 or 8 wherein the ion-exchange polymer gels in contact with the nasal mucosa.

10. A composition according to any one of the preceding claims wherein the ion-exchange material is bioadhesive.

11. A composition according to any one of the preceding claims wherein the composition contains sufficient nicotine to overload the ion-exchange material such that the excess nicotine not complexed with the ion-exchange material is delivered as a pulse.

12. A composition according to claim 3 wherein the composition comprises a mixture of ion-exchange microspheres and non-ion-exchange microspheres, the non-ion-exchange microspheres providing the pulse delivery of nicotine and the ion-exchange microspheres providing the controlled release phase.

13. A composition according to claim 1 which comprises nicotine or salt or derivative thereof incorporated in non-ion-exchange bioadhesive microspheres for controlled release together with excess nicotine, which may be adsorbed to the surface of the microspheres, for delivery as a pulse.

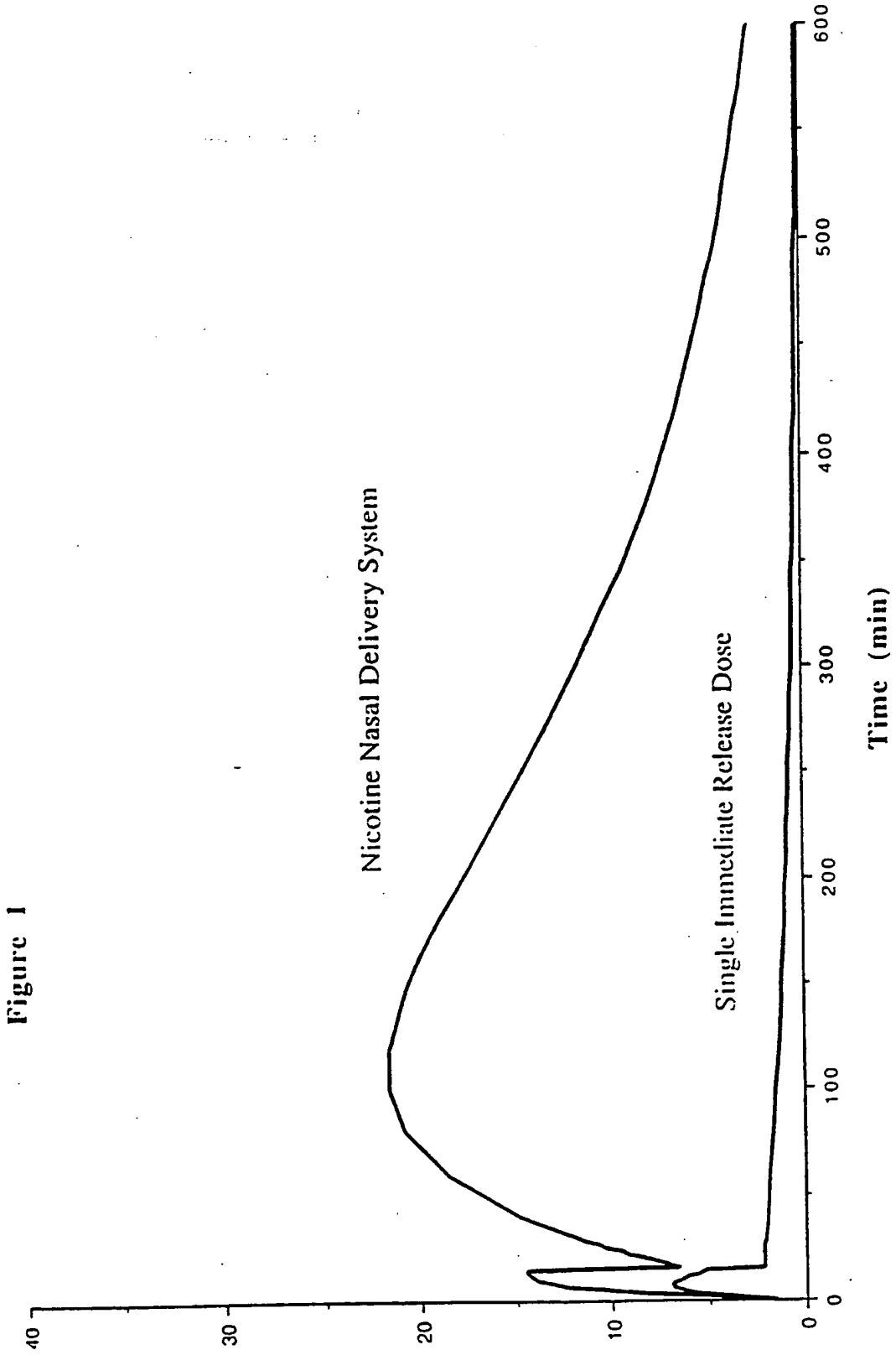

Nicotine Nasal Delivery System
Single Immediate Release Dose
Nicotine concentration (µg/l)
Time (min)
0
10
20
30
40
0
100
200
300
400
500
600

Figure 1

Figure 2

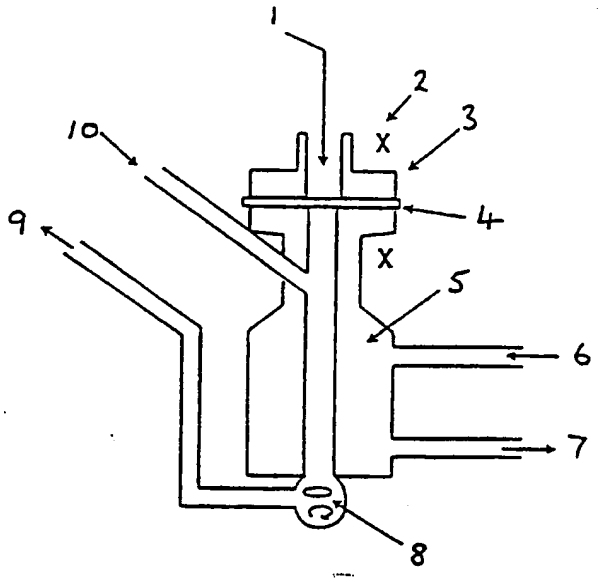
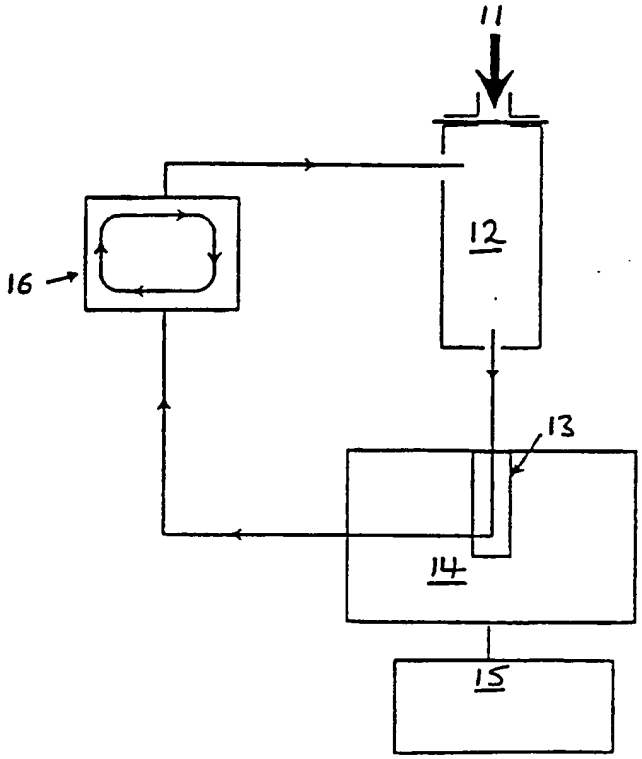


Figure 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/01092

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/00 A61K9/16 A61K47/48 A61K31/465

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 12764 (THE GOVERNORS OF THE UNIVERSITY OF ALBERTA) 8 July 1993 see claims 1-4 see example 1	1-3,7,10,11
A	EP,A,0 148 749 (ADVANCED TOBACCO PRODUCTS, INC.) 17 July 1985 see claims 1,2,9,10 see examples 1-4	1-3,11,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 1994	23.08.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/GB 94/01092

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9312764	08-07-93	AU-B- 3340393	28-07-93
EP-A-0148749	17-07-85	JP-A- 61254170	11-11-86